AD_____

Award Number: DAMD17-03-2-0024

TITLE: Physiologic and Endocrine Correlates of Overweight and Obesity in African Americans and Caucasians

PRINCIPAL INVESTIGATOR: Patricia A. Deuster, Ph.D.
Merrily Poth, M.D.
Tracey Sbrocco, Ph.D.
Martha Faraday, Ph.D.

CONTRACTING ORGANIZATION: Henry M. Jackson Foundation for the Advancement of Military Medicine
Rockville, Maryland 20852

REPORT DATE: March 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	March 2005	Annual (1 Mar 04 - 28 Feb 05)

4. TITLE AND SUBTITLE
Physiologic and Endocrine Correlates of Overweight and Obesity in African Americans and Caucasians

5. FUNDING NUMBERS
DAMD17-03-2-0024

6. AUTHOR(S)
Patricia A. Deuster, Ph.D.
Merrily Poth, M.D.
Tracey Sbrocco, Ph.D.
Martha Faraday, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Henry M. Jackson Foundation for the Advancement of Military Medicine
Rockville, Maryland 20852

E-Mail: pdeuster@usuhs.mil

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

Obesity has reached epidemic levels and yet the incidence continues to rise. The current study is seeking to examine the hypothesis that obesity may reflect dysfunctioning of the hypothalamic-pituitary-adrenal (HPA) axis in response to stressors. African American persons are at greatest risk, but reasons for this difference are unknown. We will study 120 men and women of Caucasian and African American ethnicity and examine their responses to physiologic stressors: exercise and ingestion of a meal. **Methods:** The HPA axis will be studied in some detail by using two stressor paradigms and two steroid regimens. We expect to be able to detect subtle differences in HPA axis reactivity in obese individuals and that might contribute to morbidity and perhaps even make individuals resistant to therapeutic interventions. **Results:** We have enrolled 63 participants, with 46 completed. Data collection and analyses are proceeding on schedule. Two abstracts were submitted and accepted for presentation in Summer 2005. **Conclusions:** We are on schedule for all milestones for this study and look forward to being able to answer the important questions regarding the potential role of the HPA axis in obesity.

14. SUBJECT TERMS
obesity, insulin sensitivity, glucocorticoids, metabolic syndrome, African Americans, Caucasians, exercise, meal feeding

15. NUMBER OF PAGES
9

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Introduction

Obesity has reached epidemic levels and yet the incidence continues to rise. The current study is seeking to examine the hypothesis that obesity may reflect a dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in response to stressors. African American persons are at greatest risk, but reasons for this difference are unknown. We will study 120 men and women of Caucasian (CA) and African American (AA) ethnicity to examine their responses to physiologic stressors: exercise and ingestion of a meal.

Body

Year Two:

1. *Recruit, screen, and test 10 Non-obese subjects.*

Table 1. Breakdown of Normal Weight Participants by Ethnicity

Non-Obese	CA	AA
Screened	35	23
Recruited/Enrolled	13	8
In Progress	0	1
Dropped	1	3
Completed	**12**	**4**
Total Enrolled		N = 21
Total Completed		N = 16

2. *Recruit, screen, and test 30 Overweight/Obese subjects.*

Table 2. Breakdown of Overweight/Obese Participants by Ethnicity

Overweight (OW) & Obese (OB)	CA-OW	AA-OW	CA-OB	AA-OB
Screened	21	31	12	15
Recruited/Enrolled	12	15	9	6
In Progress	0	5	3	0
Dropped	0	3	0	1
Completed	**12**	**7**	**6**	**5**
Total Enrolled OW & OB		N = 42		
Total Completed OW & OB		N = 30		

We believe that we are ahead of schedule, given that the first annual report covered only five months.

3. *Evaluate, reduce, and analyze data for first 20 subjects.*

Multiple meetings have occurred among the PI, Co-investigators, with the Project Coordinator and other key staff on a regular basis to discuss issues and examine data collected on all completed subjects. Preliminary hormone, psychological, and other physiological data have been analyzed while preparing for two different abstracts to be presented at conferences this year. We are ahead of schedule for this goal.

4. *Begin biochemical analyses.*

Radioimmunoassay (RIA) analyses have begun on several of the different hormones of interest. Specifically, assays on ACTH, Insulin, and Cortisol have begun. We have ACTH data on the first 30 subjects, Insulin on the first 9 subjects, and Cortisol on the first 12 subjects. As we continue the biochemical analyses on these hormones, we are also beginning biochemical analysis of the hormone, DHEA. We are on track for this goal.

5. *Begin statistical analyses by body mass index/BMI.*

We have complete data on 20 non-obese subjects, 22 overweight subjects, and 13 obese subjects. From preliminary analyses of these data, it is evident that fasting blood glucose, resting heart rate, and blood pressure (S: systolic; D: Diastolic) increase as a function of body mass index or BMI (Table 1). Moreover, maximal aerobic capacity decreases with increasing BMI, and is significantly lower in obese as compared to normal and overweight individuals. This confirms that obese men and women have characteristics consistent with poor cardiovascular health. We have not yet examined these data by ethnicity.

Table 3. Metabolic Parameters by BMI Category

	18 ≤BMI<25 n=20	**25≤BMI<30 n=22**	**30≤BMI<38 n=13**
Body Weight (kg)	63.2 ± 9.5	86.7 ± 11.1	101.1 ± 13.5
Glucose (mM)	71.8 ± 8.0	76.3 ± 8.4	82.1 ± 14.4
Resting HR (bpm)	66.5 ± 11.0	64.2 ± 8.9	73.4 ± 14.1
Resting Blood Pressure	S: 122 ± 12.6 D: 64 ± 8.3	S: 122 ± 8.1 D: 65 ± 6.3	S: 139 ± 14.3 D: 74 ± 9.9
Vo2Max (ml/kg/min)	48.9 ± 6.7	43.9 ± 10.7	35.2 ± 10.5

6. *Examine data on HPA reactivity from the exercise and meal challenge tests as a function of weight status after 30 overweight/obese/non-obese subjects have been tested.*

We have analyzed cortisol data on the first 12 participants (1 non-obese, 6 overweight, and 5 obese participants). It is evident that DEX is suppressing cortisol levels both at baseline and in response to the stressors (exercise and liquid meal). In contrast, HCO treatment yields a higher cortisol response to exercise than the placebo group. Not enough cortisol data are available to determine if there are differences among the three weight groups. Based on the first 12 participants, there is a large variability in cortisol levels both at baseline and in response to the exercise and meal challenge stressors.

7. *Examine data describing HPA axis resistance to feedback control and insulin resistance as a function of weight status after 20 overweight/obese and 15 non-obese subjects have been tested.*

We submitted an abstract to The Endocrine Society for their annual meeting. The abstract discussed initial data on glucose and insulin responses to placebo and DEX by BMI group. Comparison among non-obese (n=16), overweight (n=18), and obese (n=11) subjects revealed

that peak glucose responses to exercise decreased with increasing BMI: obese subjects exhibited no significant increase in serum glucose during exercise. Peak glucose in response to exercise under placebo conditions was 7.6 ± 0.4 mM in non-obese; 6.4 ± 0.4 mM in overweight; and 5.8 ± 0.4 mM in obese subjects. DEX treatment did not affect these relative differences, although baseline glucose and insulin were higher in all groups after DEX treatment.

The glucose response to the meal challenge in these subjects was comparable among the three groups. Both overweight and obese subjects showed relative insulin resistance. At least preliminarily, insulin resistance appears to be greater in obese individuals as compared to overweight participants under the DEX treatment.

8. *Examine data describing relation between exercise-associated increases in insulin sensitivity and glucocorticoid sensitivity as a function of weight after 30 overweight/obese and 15 non-obese subjects have been tested.*

Blood glucose responses to both the meal challenge and the maximal exercise challenge for participants are presented below. The figure on the left shows 52 participants categorized by BMI category, while the figure on the right shows glucose responses for 13 obese participants categorized by ethnicity. Obese individuals have higher glucose levels at almost all time points. Those differences are even more pronounced during the meal challenge, which suggests that insulin-mediated glucose disposal may be decreased in obese individuals. However, after the maximal exercise challenge, the obese group displayed glucose levels lower than their fasting glucose. This suggests that exercise may increase insulin sensitivity, particularly in obese individuals; this would lead us to believe that exercise should benefit all obese people. When analyzed by ethnicity, blood glucose responses to the meal and exercise differed between the obese AA and CA groups: the obese AA showed slightly greater glucose responses to the meal challenge than CA.

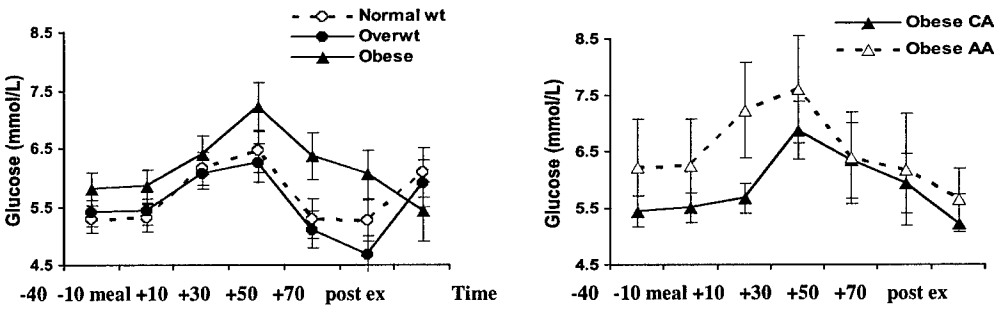

Figure 1: Glucose Values for Three Weight Groups and Two Obese Ethnic Groups with 7 Measure Points before and after a Meal, and after Exercise (Mean and S.E.M)

Key Research Accomplishments

- Screened 137 interested persons
- Prepared abstract for DOD conference in San Juan, Puerto Rico in April 2004
- Prepared abstract for American Psychological Association meeting in Washington, D.C. in August 2005
- Prepared abstract for The Endocrine Society meeting in San Diego, CA in June 2005
- Enrolled 63 participants
- Completed testing on 46 participants

- Completed biochemical analysis for ACTH on 30 subjects
- Completed biochemical analysis for Insulin on 9 subjects
- Completed biochemical analysis for Cortisol on 12 subjects
- Began biochemical analysis for DHEA
- Held a booth for recruitment and advertisement at the NBC4 Health and Fitness Expo in Washington, D.C. in January 2005

Reportable Outcomes

We prepared an abstract for the August 2005 American Psychological Association annual meeting that examined the associations among chronic stress, BMI, and ethnicity in 50 of our participants. There were 19 African-American (AA) and 31 Caucasian-American (CA) participants who completed a Stress Profile, which has subscales for chronic stress, healthy and lifestyle behaviors, and coping. Results of these 50 participants showed that chronic stress was positively related ($r = +0.67$, $p<0.05$) to BMI among AA, but not CA ($r = -0.05$, ns), and this relationship was strongest among AA women ($r = +0.72$, $p<0.05$). There was no relationship between BMI and Stress Profile subscales among CA, but BMI was significantly related to negative appraisal ($r = +0.50$, $p<0.05$), cognitive hardiness ($r = -0.59$, $p<0.05$), and psychological well being ($r = -0.48$, $p<0.05$) among AA. The data we are collecting on the HPA axis will be critical to related psychological data in a physiological context and develop a biological explanation.

Biochemical analysis of insulin has been completed on 5 overweight and 4 obese participants thus far. By using their fasting insulin and glucose data, we were able to examine insulin sensitivity in these two groups by using the insulin sensitivity check index {QUICKI = $1/[\log(\text{Insulin}) + \log(\text{Glucose})]$}. QUICKI for the overweight group was 0.352 (SD ± 0.28) and for the obese group, 0.313 (SD ± 0.004). These two groups were significantly different in their insulin sensitivity ($F(1,7) = 7.452$, $p<0.05$). The study criteria we set exclude anyone with significant health problems, including diabetes. However, the QUICKI score for the obese group was comparable to that of individuals with diagnosed glucose intolerance. This may suggest that individuals with obesity (BMI between 30 and 38) have markedly reduced insulin sensitivity.

Biochemical analysis of ACTH has been completed on 6 non-obese, 8 overweight, and 5 obese participants. While large variability exists among participants within a BMI category, it appears there is a trend towards the non-obese participants showing a greater increase in ACTH in response to both maximal and submaximal exercise. A cursory glance indicates that overweight and obese participants elicit similar responses to both types of exercise. However, none of the BMI groups show any response to the meal challenge after exercise. Finally, DEX appears to suppress ACTH in the overweight and obese participants, while some non-obese participants may escape suppression and have high ACTH levels following exercise. This is very preliminary and the data have not been statistically evaluated.

Conclusions

African Americans (AA) have the highest coronary heart disease mortality of any ethnic group in the United States, and AA women have a higher prevalence of Metabolic Syndrome than CA women. Our preliminary data indicate that obese men and women have several characteristics consistent with poor cardiovascular health, including lower maximal aerobic capacities and higher resting blood pressure, heart rates, and fasting glucose levels. In response

to the meal challenge obese participants show higher blood glucose levels during the meal challenge. Interestingly, blood glucose levels decrease with an acute bout of exercise suggesting that aerobic exercise may have some beneficial effects on insulin sensitivity in obese persons. Examining the blood glucose data by ethnicity showed some different and interesting responses following the meal and exercise challenges. Obese AA showed slightly greater glucose responses to the meal challenge than CA.

When fasting insulin and glucose data were used to determine insulin sensitivity, scores for our obese participants were comparable to individuals with diagnosed glucose intolerance. Based on this observation, it is possible that obese individuals have markedly reduced insulin sensitivity, despite normal fasting glucose levels. In addition, data submitted on one of our abstracts suggests that insulin resistance appears to be greater in obese individuals as compared to overweight participants under the DEX treatment.

Finally, our abstract submitted with data from the stress profile shows that chronic stress is positively related to BMI among AA, but not CA participants. Further, BMI is significantly related to negative appraisal, cognitive hardiness, and psychological well being among AA, but not CA women. These data suggest that the physiological responses of the HPA axis may be related to psychological state in AA and CA persons.

Our goals for year two of this study included testing more participants, analyzing data, continuing biochemical and statistical analyses, and examining data for HPA reactivity, resistance to feedback control and insulin resistance, and exercise-associated increases in insulin and glucocorticoid sensitivity. We have successfully met these goals and are ahead of schedule in many areas. Despite only testing participants for 17 months, we have enrolled over 60 to date and have completed testing of 46 participants. We also submitted two abstracts and gave one poster presentation based on our physiological, biochemical, and psychological testing. Over the next two years we will continue to examine differences between CA and AA in terms of potential underlying causes of the metabolic syndrome and how different physiologic stressors activate the HPA axis and metabolic processes intrinsic to obesity and associated CHD risk factors.

References

1. Cossrow N, Falkner B. Race/ethnic Issues In obesity and obesity-related comorbidities. J Clin Endocrinol Metab. 2004; 89(6):2590-4.
2. Ferdinand KC, Clark LT. The epidemic of diabetes mellitus and the metabolic syndrome In African Americans. Rev Cardiovasc Med. 2004;5 Suppl 3:S28-33.
3. Hall WD, Clark LT, Wenger NK, Wright JT Jr, Kumanyika SK, Watson K, Horton EW, Flack JM, Ferdinand KC, Gavin JR 3rd, Reed JW, Saunders E, O'Neal W Jr; African-American Lipid and Cardiovascular Council. The Metabolic Syndrome in African Americans: a review. Ethn Dis. 2003;13(4):414-28.
4. Yancey AK, Jordan A, Bradford J, Voas J, Eller TJ, Buzzard M, Welch M, McCarthy WJ. Engaging high-risk populations in community-level fitness promotion: ROCK! Richmond. Health Promot Pract. 2003;4(2):180-8.
5. Velasquez-Mieyer PA, Cowan PA, Umpierrez GE, Lustig RH, Cashion AK, Burghen GA. Racial differences in glucagon-like peptide-1 (GLP-1) concentrations and insulin dynamics during oral glucose tolerance test in obese subjects. Int J Obes Relat Metab Disord. 2003;27(11):1359-64.
6. Patt MR, Yanek LR, Moy TF, Becker DM. Assessment of global coronary heart disease risk in overweight and obese African-American women. Obes Res. 2003;11(5):660-7.

Appendices

None